Chemical Translations

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CERTIFICATE OF ACCURACY

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TRANSLATION FROM *German*

On this day, I **S. Edmund Berger** state:

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as submitted to me in the

German language;

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The attached items are a correct and accurate reproduction of the original documents concerning this patent application.

Munich, May 07, 2003

[Seal]

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For The President

[Signed:]
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High-affinity Cosmetic Agents

The present invention relates to cosmetic agents comprising two components covalently linked to one another and with functions that differ from one another, the first component being a peptidic linker molecule of high affinity or binding specificity for keratin-containing material and the second component being at least one cosmetically active substance, consisting of at least one known cosmetically active compound or cosmetic effector molecule for cosmetic treatment of keratin-containing material.

In general, the combination of the invention finds use in the cosmetic treatment of keratin-containing parts of the human or animal body, particularly as a hair-treatment agent.

The goal-oriented and in terms of quantity and manner optimal use of cosmetic products is based on the idea that it should be possible to apply such agents or active substances to the desired sites of the body as efficiently as possible while excluding other areas from them as much as possible.

In principle, three methods are available to achieve this goal. By one method, a cosmetic substance exerting the desired action is applied locally to the desired site of the body with the aid of suitable mechanical means while simultaneously covering areas of the body that are not to come in contact with the said cosmetic substance. This method, however, has the drawback that only directly accessible areas of the body can be reached, that contact of undesirable body sites can practically not be excluded and that handling of the method is troublesome.

Another method is based on the possibility of selecting, on the basis of certain chemical andbiochemical/physiological properties, cosmetically active substances that preferen-tially bind or adhere to certain structures (for example skin, hair or nails). The drawback of these methods lies, in particular, in that the use of these substances is narrowly limited by their chemical composition so that the desired site-specific action of the cosmetic agent involved often does not take place in the desired manner and that the agent is unsuitable for cosmetic use.

As a third possibility, it has recently been proposed to use various antibodies with different specificity for cosmetically active substances as vehicles for a goal-oriented application of

cosmetically active substances. In this manner, by coupling with antibodies, the cosmetically active substances are supposed to be transported to the desired sites. A particular drawback of such methods is that the preparation of the antibodies is very expensive and that antibodies are relatively large, complicated and biologically active protein units the use of which from a biochemical as well as physiological standpoint is known not to be without problems.

The objective of the present invention was to provide cosmetic agents and new methods of cosmetic treatment that would eliminate the disadvantages of the prior art.

This objective was reached in accordance with claim 1 by preparing a high-affinity cosmetic agent which comprises two components covalently bound to one another and having functions that differ from one another, the first component being a peptidic linker molecule with high affinity or binding specificity for keratin-containing material and the se-cond component being at least one cosmetically active substance consisting of at least one known organic cosmetically active compound or an organic cosmetically active ef-fector molecule.

Surprisingly, we have now found that peptides with a chain length between 2 and 30 amino acids, preferably between 6 and 15 amino acids and particularly between 6 and 12 amino acids can, on the one hand, bind specifically to keratin-containing materials, particularly hair, and, on the other, be linked with cosmetically active substances in a manner such that the said cosmetically active substance can be applied to keratin-containing material (particularly hair) in an advantageous fashion via the said peptidic linker molecule.

In this manner, a cosmetic agent is obtained which consists of two components covalently bound to each other, namely a peptidic linker molecule with bonding specificity for keratin or keratin-containing material and at least one cosmetic active substance bound thereto. In this case, the peptidic linker molecule acts as binding agent and vehicle for the cosmetically active substance, it also being possible for several cosmetically active substances to be bound to the same peptidic linker. In this manner one obtains a cosmetic agent with high affinity for keratin-containing material, particularly for animal and human hair.

Another object of the present invention is the use of the said cosmetic agent for cosmetic treatment of keratin-containing material and the use of the said peptidic linker molecules

and effector molecules for preparing a cosmetic agent with high affinity or binding specificity for keratin or keratin-containing material.

The cosmetic agent of the invention has a number of advantages. Particularly noteworthy among them are the goal-oriented use of cosmetically active substances (dyes, cosmetic care-imparting preparations, conditioners) so that they can exert their action essentially only on specific and desired sites of the body, particularly on hair. Moreover, this results in a stronger and longer-lasting adherence of the cosmetically active substance to the application site, particularly the hair, and in the fact that depending on the bonding strength of the peptidic linker molecule a controllable or controlled retention time or intensity of the cosmetically active substance, for example a dye, can be obtained. An additional advantage is that a lower amount of the cosmetically active substance is consumed.

Furthermore, with the cosmetic agent of the present invention it is possible to achieve a combination of several advantageous properties with the same product. For example, via the peptidic linker an effector molecule exerting a hair-care action can be linked with a hair-dye molecule so that a hair-care and hair-dyeing product can be provided at the same time. Or a peptidic linker itself can exert cosmetic care properties so that with just a single linking of, for example, a color-producing effector molecule to the peptidic linker it is possible to attain cosmetic care and dyeing properties at the same time. With the cosmetic agent of the invention it is thus possible to achieve two different cosmetic effects.

An additional advantage of the cosmetic agent of the invention is that it shows highly pronounced variability that can also be controllable. For example, different peptidic link-ers which can also present differently pronounced bonding strengths to keratin-containing material can be combined with entirely different effector molecules, for example a sur-face-active substance and a hair dye. In this case, it is possible to create a cosmetic agent in which the effector molecules, as a result of the different bonding properties of "their" peptidic linkers, can have an individual retention time or exert individual properties at the application site.

Moreover, compared to healthy hair, hair damaged by mechanical effects (for example by combing or rubbing), chemical effects (for example, dyeing, bleaching, waving or uncurling) or physical effects (UV radiation, weathering effecfs) can have different bonding strengths and bonding sites for the peptidic linker. In such cases, a cosmetic agent of the

invention can preferentially and particularly strongly bond to damaged areas of the hair, for example to hair ends damaged by splicing, by the fact that the peptidic linker molecule bonds with a cosmetic-care effector molecule and/or a coloring effector molecule and/or an effector molecule that acts as a UV filter bonds.

From this, persons skilled in the art can clearly see the advantages offered by the present invention in preparing a multitude of cosmetic agents with advantageously combined properties.

For purposes of the present invention, by "keratin-containing material" are meant the skin and skin appendages, for example the scalp hair, eyebrows, eyelashes, toenails and finger nails of the animal and human body.

By "peptidic linker molecule" are meant for purposes of the present invention polymers the monomers of which consist of amino acids that are usually linked to each other by acid amide bonds. They can be of synthetic origin (prepared by total industrial synthesis), semisynthetic origin (obtained by partial synthesis from natural sources) or natural origin and they include genetic engineering methods of preparation (for example the known methods of DNA recombination, phage-peptide libraries or phage display).

By "cosmetic active substance" or "cosmetically active compound" or "cosmetic effector molecule" are meant compounds, substances or molecules for which it is known that they exert a cosmetic effect on the surface of an animal or human body, particularly those with dyeing or coloring, cosmetic care, conditioning, protecting, hardening, softening, repairing and/or reconstituting properties. In the following, only the term "effector molecule" will be used as a synonym for "cosmetic active substance" or "cosmetically active compound".

In this regard, the present invention also relates to the use of a peptidic linker molecule and at least one organic cosmetically active effector molecule with dyeing or coloring, cosmetic care, conditioning, protective, hardening, softening, repairing and/or reconsti-tuting property for producing a cosmetic agent.

The coupling of a peptidic linker molecule to an effector molecule can be undertaken by use of chemical methods that in and of themselves are known.

Preferably used peptidic linker molecules are glycine or glycine derivatives containing heteroatoms or heteroatom groupings that are suitable for bonding with the effector molecules. Suitable glycine derivatives are alpha-amino acids with at least three carbon atoms, the suitable heteroatoms or heteroatom groups, for example an amino, hydroxyl, sulfanyl or carboxyl group, preferably being attached to the terminal carbon atom.

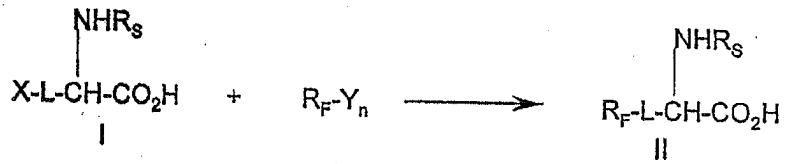
Preferably used as effector molecules are dyes of dye precursors containing a reactive group capable of forming a covalent bond with the heteroatoms or heteroatom groups.

Suitable reactive groups are, for example, triazinyl, sulfatoethylsulfonyl or vinylsulfonyl groups. It is also possible, however, to use halogenopyrimidine, chloracetamido, carbamate, epoxide or methylol groups as the reactive groups.

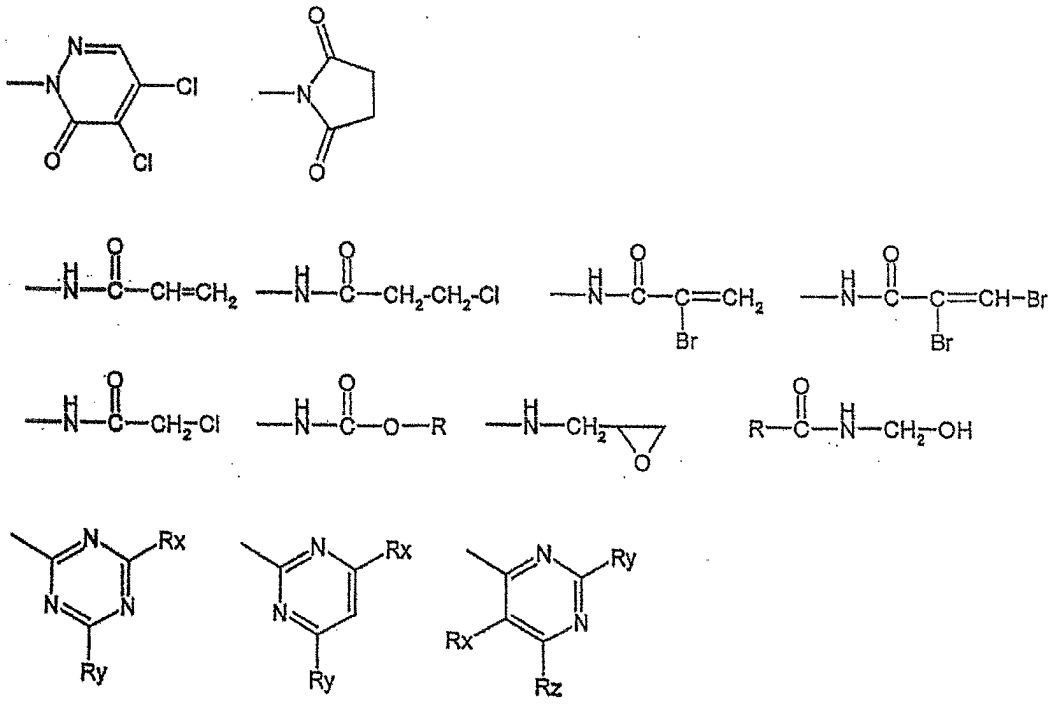
Suitable dye precursors are, for example, halogenonitroaromatics such as 2,4-dinitrofluorobenzene, 2,6-dinitrofluorobenzene or 4-fluoro-3-nitroaniline.

The coupling reaction of an effector molecule can take place, for example, by the fol-lowing scheme, a dye or dye precursor in this exemple being the effector molecule.

Glycine derivatives of formula I can be condensed with dyes or dye precursors R_F-Y that contain a suitable reactive group to form dyes of formula II by the following reaction scheme:



wherein R_F denotes a dye or dye precursor, R_S denotes a hydrogen atom or a t-butoxycarbonyl (Boc) group, L stands for an alkylene group or a phenylene group, X de-notes an amino, hydroxyl or sulfanyl group and Y is selected from among a halogen atom (F, Cl, Br) or one of the following atom groupings:



wherein R_x, R_y and R_z independently of each other denote F, Cl, Br or an NR1R2, an OR1 or an SR1 group provided that the R1 and R2 independently of each other denote a hydrogen atom, a straight-chain or branched C1-C6 alkyl group, an aromatic or hetero-aromatic ring with 5-6 ring atoms or a fully or partly saturated ring compound with 5 to 7 ring atoms.

Suitable derivatives of the amino acids of formula I are preferably compounds containing a free amino, hydroxyl or sulfanyl group, for example the derivatives of 3-aminoalanine, ornithine, lysine, serine, threomine [sic], cysteine and homocysteine.

Discovering and selecting a peptidic linker molecule that is suitable for the purpose of the present invention and shows bonding specificity for keratin-containing material can be accomplished by known methods and is trivial for those skilled in the art.

The peptidic linker molecules and masked amino acids that are suitable for the present invention can be prepared by methods that in and of themselves are known or are com-

mercially available, for example, from the ORPEGEN Pharma company, Heidelberg. It is thus possible to synthesize a peptide of the desired chain length of, for example, 10 ami-no acids by routine methods, for example by the generally known Merrifield technique.

The selection of the amino acids suitable for the synthesis of the peptide preferably depends on their charges or on the arrangement of charged amino acid side groups and/or amino acid side groups capable of hydrogen. In this respect, we can mention, for example, glutamic acid, aspartic acid, arginine, histidine, tyrosine, threonine and lysine.

Suitable peptides can also be identified by screening phage-peptide libraries (a method also known as phage display), for example as indicated by Devlin J. J. et al., Science 249, 404-406 (1990) and possible further optimization thereof by the cosmix plexing method according to WO 98/33901.

The selection of peptides that are suitable as peptidic linker molecules and have a sufficiently high bonding affinity for keratin-containing material can be accomplished by known methods. For example, this can be done by bringing a keratin-containing material, preferably hair, in contact with at least one linker-effector molecule combination according to the present invention. This can be done, for example, by dipping a hair sample at room temperature (20 to 22 °C) into an aqueous solution having a pH from 5 to 6 and in which is present a combination of a peptidic linker and a colored effector molecule (6-((4-amino-2-nitrophenyl)amino)-(2S)-2-(((1,1-dimetylmethoxy)carbonyl)amino)hexanoic acid). After a reaction time of about 2 to 10 minutes, the bonding of the effector molecule to the hair can be evaluated by washing tests with a common hair detergent (shampoo).

The bonding affinity of the peptidic linker molecules suitable for the invention to keratin-containing material is not critical. Comprised according to the invention are peptidic linkers exerting specific bonding to keratin-containing material in aqueous solution in the pH range between pH 4.0 and pH 8.5 and preferably between pH 5.0 and 6.0 and which, in comparison with a sample with, for example, a simple hair dye without peptidic linker, would withstand at least four common hair washings with conventional shampoos without an appreciable loss in efficacy.

The higher the affinity of the peptidic linker the stronger is the adherence of the said cosmetic agent at the desired application site.

Through the choice of the peptidic linker on the basis of its affinity to keratin or keratin-containing material, the cosmetic material can exert a more or less strong adherence at the application site so that as a result of the present invention the said effector molecules can be linked with different strength, adherence or durability. In this manner, it becomes possible to provide cosmetic agents that are adapted quite differently to the individual retention time requirements.

As already indicated, the term effector molecule includes substances which on the sur-face of an animal or human body exert a cosmetic activity, particularly those with dyeing or coloring, cosmetic care, conditioning, protecting, hardening, softening, repairing and/or reconstituting properties.

Suitable for the present invention mainly as cosmetic care and/or conditioning and/or protective effector molecules are all substances that are known to show on the skin or body appendages, particularly hair, properties which can include hardening, softening, repairing or reconstituting effects. These include, for example: combability improvers, for example cationic polymers (for example Iniquat FC 370, Jaguar C-162, Polymer JR 125), protein hydrolyzates (for example those derived from wheat), cationic surfactants (for ex-ample cetyltrimethylaminium chloride, distearylammonium chloride), amidoamines, beta-ine esters; Esterquats; luster-imparting agents, for example silicone polyols and fatty alco-hols, volume-imparting agents such as chitosan, moisturizers, such as the lactates (for example cetyl lactate); vitamins, provitamins or vitamin precursors, for example panthenol and the derivatives thereof, biotin, tocopherols, springiness improvers, for example betain and derivatives thereof, sugars, for example polysaccharides, oligosaccharides, glucose, fructose or inulin, organic-chemical UV filters with all UVA-, UVB- and UVA/UVB filter substances being suitable, either individually or in combination, for example the derivatives of dibenzoylmethane (for example Parsol 1789 supplied by Givaudan/Roure, INCI designation: butyl methoxydibenzoylmethane), benzyldicamphor or derivatives thereof, particularly methylbenzylidenecamphor (for example 3-benzylidenecamphor, 3-(4-methylenebenzylidene)dicamphor), derivatives and esters of cinnamic acid, particularly the derivatives and esters of methoxycinnamic acid (for example octyl 4-methoxycinnamate or isopentyl 4-methoxycinnamate), derivatives and esters of benzoic acid, particularly of 4-aminobenzoic acids, polyhydroxybenzoic acids (for example methyl polyhydroxybenzoate or propyl polyhydroxybenzoate), esters of salicylic acid (for example 2-ethylhexyl salicyl-ate or 4-isopropylbenzyl salicylate), sulfonic acids, benzophenones and the derivatives thereof,

for example the sulfonic acid derivatives of benzophenone (for example 2-hydro-xy-4-methoxybenzophenone-5-sulfonic acid) as UVB/UVA filters or of the benzimida-zoles (for example 2-phenylbenzimidazole-5-sulfonic acid) and the salts thereof, diben-zoylmethane or suitable polypeptides, particularly oxygen radical scavengers, for example the known Mn-, Fe- or Zn peroxide dismutases, as well as tocopherols and vitamins (for example ascorbic acid).

The cosmetic agent of the invention can contain the said cosmetic care agents and/or conditioning and/or protective effector molecules in a total amount between 0.001 to 30.0 wt.%, particularly between 0.01 and 25.0 wt.%, more particularly between 0.1 to 15 wt.% and preferably between 0.5 and 10.0 wt.%, based on the amount of the cosmetic agent.

Also suitable are synthetic polymers, particularly the acrylic polymers from the group of crosspolymers of acrylates and alkyl acrylates and/or acrylates and allyl ethers. Suitable to this end are, for example, Permulen®, Carbopol® and Acrisint® brands, for example Permulen TR1 by Goodrich (INCI designation: acrylates/C10-30 alkyl acrylate cross-polymer), Carbopol 1382 by Goodrich (INCI designation: acrylates/C10-30 alkyl acrylates crosspolymer), Carbopol 2984 by Goodrich (INCI designation: carbomer) or Carbopol Ulrez 10 by Goodrich (INCI designation: carbomer) or Acrisint 400 by 3 V (INCI desig-nation: carbomer), which can be present in the cosmetic agent of the invention either alone or in combination.

Such polymers can be present in the cosmetic agent in a total amount between 0.05 and 5.0 wt.%, particularly between 0.1 and 3.0 wt.% and most particularly between 0.1 and 1.0 wt.%, based on the total amount of the cosmetic agent.

Suitable dyes or coloring effector molecules are all oxidative, nonoxidative, direct, natural, synthetic and semisynthetic dyes which from a cosmetic standpoint find use in the dyeing or tinting of keratin-containing materials, particularly hair. The direct dyes are preferred. Particularly well suited for this purpose are nitro dyes, azo dyes, quinone dyes, triphenyl-methane dyes and acid and basic dyes of different colors.

Other suitable dyes are the reactive dyes containing a triazinyl, sulfatoethylsulfonyl or vi-nylsulfonyl group, for example Reactive Blue 2, Reactive Blue 19, Reactive Red 2, Re-active Orange 16, Reactive Black 5 and Reactive Yellow 2.

Dye precursors can also be used. Suitable dye precursors are, for example, halogenonitrobenzene derivatives that can be reacted with compounds having free amino or hydro-xyl groups to form nitro dyes. Examples of these are 4-fluoro-3-nitroaniline, 5-fluoro-2-nitroaniline, 1-chloro-2,4-dinitrobenzene and 1-fluoro-2,4-dinitrobenzene.

Blue nitro dyes are, for example:
1,4-bis[(2'-hydroxyethyl)amino]-2-nitrobenzene,
1-(2'-hydroxyethylamino]-2-nitro-4-bis-(2"-hydroxyethyl)aminobenzene (HC Blue No.2),
1-amino-3-methyl-4-(2'-hydroxyethyl)amino-6-nitrobenzene (HC Violet No. 1),
4,N-ethyl,N-(2"-hydroxyethyl)amino-1-(2"-hydroxyethyl)amino-2-nitrobenzene hydrochloride (HC Blue No. 12),
4-bis-(2'-hydroxyethyl)amino-1-(2"-methoxyethyl)amino-2-nitrobenzene (HC Blue No. 11),
1-(2',3'-dihydroxypropyl)amino-4-[N-methyl-(2"-hydroxyethyl)amino]benzene hydrochloride (HC Blue No. 10),
1-[(2',3'-dihydroxypropyl)amino]-2-nitro-4-[N-ethyl-2"-(hydroxyethyl)amino]benzene hydrochloride (HC Blue No. 9),
1-(3'-hydroxypropylamino)-2-nitro-4-bis-(2"-hydroxyethylamino)benzene (HC Violet No. 2),
4,N-methyl,N-(2',3'-dihydroxypropyl)amino-1-methylamino-2-nitrobenzene hydrochloride (HC Blue No. 6),
4'-amino-2'-nitro-2"-carboxy-4"-dimethylaminodiphenylamine (HC Blue No. 13).

Red nitro dyes are, for example:
1-amino-4-(2'-hydroxyethyl)amino-2-nitrobenzene (HC Red No. 7),
1-hydroxy-2-amino-4,6-dinitrobenzene,
4-amino-2-nitrodiphenylamine (HC Red No. 1),
1-amino-2-nitro-4-bis-(2'-hydroxyethyl)aminobenzene hydrochloride (HC Red No. 13),
1-amino-2-nitro-4-(2'-hydroxyethyl)amino-5-chlorobenzene,
1-(2'-hydroxyethyl)amino-2-nitro-4-aminobenzene (HC Red No. 3),
1-hydroxy-3-nitro-4-aminobenzene,
1-hydroxy-3-nitro-4-(2'-hydroxyethylamino)benzene,
1-(2'-aminoethyl)amino-2-nitro-4-(2'-hydroxyethoxy)benzene (HC Orange No. 2),
3-nitro-4-(2'-hydroxyethyl)aminophenyl glycerol ether (HC Orange No. 3),
1-amino-5-chloro-4-(2',3'-dihydroxypropylamino)-2-nitrobenzene (HC Red No. 10),
1,4-bis-[(2',3'-dihydroxypropyl)amino]-5-chloro-2-nitrobenzene (HC Red No. 11),
1-hydroxy-2-(2'-hydroxyethyl)amino-4,6-dinitrobenzene,

3-nitro-4-ethylaminobenzoic acid,
4-amino-2-nitrodiphenylamino-2-carboxylic acid,
2-chloro-6-ethylamino-4-nitrophenol,
2-amino-6-chloro-4-nitrophenol,
1-hydroxy-3-nitro-4-(3'-hydroxypropylamino)benzene,
2,5-diamino-6-nitropyridine,
1,2,3,4-tetrahydro-6-nitroquinoxaline,
7-amino-3,4-dihydro-6-nitro-2H-1,4-benzoxazine (HC Red No. 14)

Yellow nitro dyes are, for example:
1-amino-2-(2'-hydroxyethyl)amino-5-nitrobenzene (HC Yellow No. 5),
1-(2'-hydroxyethoxy)-2-(2"-hydroxyethyl)amino-5-nitrobenzene (HC Yellow No. 4),
1-(2'-hydroxyethyl)amino-2-nitrobenzene (HC Yellow No. 2),
1-methoxy-2-(2'-hydroxyethyl)amino-5-nitrobenzene,
1-hydroxy-2-amino-3-nitrobenzene,
1-amino-2-methyl-6-nitrobenzene,
1-(2'-hydroxyethyl)oxy-3-methylamino-4-nitrobenzene,
1-methylamino-2-nitro-5-(2',3'-dihydroxypropyl)oxybenzene,
1-(2'-hydroxyethyl)amino-2-hydroxy-4-nitrobenzene (HC Yellow No. 11),
1-methoxy-3-(2'-aminoethyl)amino-4-nitrobenzene hydrochloride (HC Yellow No. 9),
1-(2'-ureidoethyl)amino-4-nitrobenzene,
4-(2',3'-dihydroxypropyl)amino-3-nitrotrifluoromethylbenzene (HC Yellow No. 6),
2,4-bis-[N-(2'-hydroxyethyl)amino]-5-chloronitrobenzene (HC Yellow No. 10),
4-(2'-hydroxyethyl)amino-3-nitromethylbenzene,
4-(2'-hydroxyethyl)amino-3-nitrochlorobenzene (HC Yellow No. 12),
4-(2'-hydroxyethyl)amino-3-nitrotrifluoromethylbenzene (HC Yellow No. 13),
4-(2'-hydroxyethyl)amino-3-nitrobenzonitrile (HC Yellow No. 14),
4-(2'-hydroxyethyl)amino-3-nitrobenzamide (HC Yellow No. 15).

Azo dyes are, for example:
1-(4'-nitrophenylazo)-2-methyl-4-bis-(2'-hydroxyethyl)aminobenzene,
1-(3'-nitro-4-amino)phenylazo-2-hydroxy-7-trimethylammoniumnaphthalene chloride,
1-(2'-hydroxy-4'-sulfo-6'-nitro)naphthylazo-2-hydroxynaphthalene CI 15700,
1-(4'-aminophenylazo)-2-methyl-4-bis-[(2'-hydroxyethyl)amino]benzene,
5-(4'-dimethylaminophenylazo)-1,4-dimethyltriazonium chloride,

1-(2'-methoxyphenylazo)-2-hydroxy-7-trimethylammoniumnaphthalene chloride,
1-(4'-aminophenylazo)-2-hydroxy-7-trimethylammoniumnaphthalene,
4-(3'-trimethylammoniumphenylazo)-N-phenyl-3-methylpyrazolone (5),
4-(hydroxy-3-[(4'-sulfo-1'-naphthyl)azo]-1-naphthalenesulfonic acid,
1-(4'-sulfophenylazo)-2-hydroxynaphthalene,
1-(4'-sulfophenylazo)-2-hydroxy-6-sulfonaphthalene CI 15985
4-amino-[4'-bis-(2"-hydroxyethyl)amino]azobenzene,
4-amino-[4'-bis-(2"-hydroxyethyl)amino]-2'-methylazobenzene,
3-(2',6'-diaminopyridyl-3'-azo)pyridine,
7-phenylazo-1-amino-3,6-disulfo-8-hydroxynaphthalene,
5-acetylamino-4-hydroxy-3-[(2'-methylphenyl)azo]-2,7-naphthalenedisulfonic acid,
2-(2',4'-dimethylphenylazo)-6-(4"-sulfophenylazo)-1,3-dihydroxybenzene.

Quinone dyes are, for example:
1,4-bis-(2',3'-dihydroxypropyl)aminoanthraquinone,
1-methylamino-4-(2'-hydroxyethyl)aminoanthraquinone,
2-(2'-aminoethyl)aminoanthraquinone,
2-bromo-4,8-diamino-6-(3'-trimethylammonium)phenylamino-1,5-naphthoquinone,
1-(2'-sulfo-4'-methylphenyl)amino-4-hydroxyanthraquinone,
1,4-diaminoanthraquinone,
1-amino-2-sulfo-4-cyclohexylaminoanthraquinone,
1-methylamino-4-aminopropylaminoanthraquinone,
1-aminopropylaminoanthraquinone,
1,4-diamino-2-methoxyanthraquinone,
1,4-bis-(2-hydroxyethyl)amino-5,8-dihydroxyanthraquinone.

Triphenylmethane dyes are, for example:
4',4",4'"-triamino-3-methyltriphenylcarbonium chloride,
bis-(4,4-diethylaminophenyl)-4'-ethylaminonaphthylcarbonium chloride,
bis-(4,4-dimethylaminophen)-4'-phenylaminonaphthylcarbonium chloride, Basic Blue 26, CI 44045 and
4,4-bis-(N-ethyl-3-sulfobenzyl)amino-2"-sulfofuchsonium.

Acid dyes are, for example:
1-(4'-sulfophenylazo)-2-hydroxy-6-sulfonaphthalene CI 15985,

1-(2'-hydroxy-4'-sulfo-6'-nitro)naphthylazo-2-hydroxynaphthalene CI 15700,
2,4-dinitro-1-naphthol-7-sulfonic acid disodium salt (Acid Yellow 1; CI 10316),
2-(2'-quinolyl)-1H-indene-1,3(2H)-dione monosulfonic acid disodium salt (Acid Yellow 3; CI 47005),
4,5-dihydro-5-keto-1-(4'-sulfophenyl)-4-[(4"-sulfophenyl)azo]-1H-pyrazol-3-carboxylic acid trisodium salt (Acid Yellow 23; CI 19140),
3',6'-dihydroxyspiro[isobenzofuran-1(3H),9'(9H)-xanthen]-3-one (Acid Yellow 73; CI 45350:1),
5-[2',4'-dinitrophenylamino]-2-(phenylamino)benzenesulfonic acid sodium salt (Acid Orange 3; CI 10385);
4-[(2',4'-dihydroxyphenyl)azo]benzenesulfonic acid sodium salt (Acid Orange 6; CI 14270);
4-[2'-hydroxy-1'-naphthyl)azo]benzenesulfonic acid sodium salt (Acid Orange 7; CI 15510);
4-{[3'-[(2",4"-dimethylphenyl)azo]-2',4'-dihydroxyphenyl]azo}benzenesulfonic acid sodium salt (Acid Orange 24; CI 20170),
4-hydroxy-3-[(4'-sulfo-1'-naphthylazo]-1-naphthalenesulfonic acid disodium salt (Acid Red 14; CI 14720),
7-hydroxy-8-[(4'-sulfo-1'-napthyl)azo]-1,3-naphthalenedisulfonic acid trisodium salt (Acid Red 18; CI 16255),
3-hydroxy-4-[(4'-sulfo-1'-naphthyl)azo]-2,7-naphthalenedisulfonic acid trisodium salt (Acid Red 27; CI 16185),
5-amino-4-hydroxy-3-phenylazo-2,7-naphthalenedisulfonic acid disodium salt (Acid Red 33; CI 17200),
5-(acetylamino)-4-hydroxy-3-[(2'-methylphenyl)azo]-2,7-naphthalenedisulfonic acid disodium salt (Acid Red 35; CI 18065),
3',6'-dihydroxy-2',4',5',7'-tetraiodospiro[isobenzofuran-1(3H),9'(9H)-xanthen]-3-one disodium salt (Acid Red 51; CI 45430),
3,6-bis-(diethylamino)-9-(2',4'-disulfophenyl)xanthylium hydroxide sodium salt (Acid Red 52; CI 45100
7-hydroxy-8-{[4'-(phenylazo)phenyl]azo}-1,3-naphthalenedisulfonic acid disodium salt (Acid Red 73; CI 27290),
2',4',5',7'-tetrabromo-3',6'-dihydroxyspiro[isobenzofuran-1(3H),9'(9H)-xanthen]-3-one disodium salt (Acid Red 87; CI 45380),
2',4',5',7'-tetrabromo-4,5,6,7-tetrachloro-3',6'-dihydroxyspiro[isobenzofuran-1(3H),9'(9H)-

xanthen]-3-one disodium salt (Acid Red 92; CI 45410),
3',6'-dihydroxy-4',5'-diiodospiro[isobenzofuran-1(3H),9'(9H)-xanthen]-3-one disodium salt (Acid Red 95; CI 45425; Acid Red 195; Acid Blue 9; CI 42090),
2,2'-[(9,10-dihydro-9,10-diketo-1,4-anthracenediyl)diimino]-bis-(5-methylbenzenesulfonic acid) disodium salt (Acid Green 25; CI 61570),
N-[4-{[4'-(dimethylamino)phenyl]-(2"-hydroxy-3",6"-disulfo-1"-naphthyl)methylene}-2,5-cyclohexadien-1-ylidene]-N-methylmethanaminium hydroxide (Acid Green 50; CI 44090,
N-{4-[[(4'-diethylamino)phenyl]-(2",4"-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene}-N-ethylethanaminium hydroxide sodium salt (Acid Blue 1; CI 42045),
N-{4-[[(4'-diethylamino)phenyl]-(5"-hydroxy-2",4"-disulfophenyl)methylene]-2,5-cyclohexadien-1-ylidene}-N-ethylethanaminium hydroxide calcium salt (Acid Blue 3; CI 42051),
1-amino-4-(cyclohexylamino)-9,10-dihydro-9,10-diketo-2-anthracenesulfonic acid sodium salt (Acid Blue 62; CI 62045),
2-(1',3'-dihydro-3'-keto-5'-sulfo-2'H-indol-2'-ylidene)-2,3-dihydro-3-keto-1H-indol-5-sulfonic acid disodium salt (Acid Blue 74; CI 73015),
9-(2'-carboxyphenyl)-3-[(2"-methylphenyl)amino]-6-[(2'"-methyl-4'"-sulfophenyl)amino)]-xanthylium hydroxide sodium salt (Acid Violet 9; CI 45190),
2-[(9',10'-dihydro-4'-hydroxy-9',-10'-diketo-1'-anthracenyl)amino]-5-methylbenzenesulfonic acid sodium salt (Acid Violet 43; CI 60730),
3,3'-[sulfonyl-bis-(2-nitro-4,1-phenylene)imino]-bis-[6-phenylamino)benzene disodium sulfonate] (Acid Brown 13; CI 10410),
4-amino-5-hydroxy-3-[(4'-nitrophenyl)azo]-6-(phenylazo)-2,7-naphthalenedisulfonic acid disodium salt (Acid Black 1; CI 20470),
3-hydroxy-4-[(2'-hydroxy-1'-naphthyl)azo]-7-nitro-1-naphthalenesulfonic acid sodium salt (Acid Black 52; CI 15711),
3-[(2,4-dimethyl-5-sulfophenyl)azo]-4-hydroxy-1-naphthalenesulfonic acid (Ponceau SX, CI 14700).

Basic dyes are, for example:
bis-(4,4-dimethylaminophen)-4'-phenylaminonaphthylcarbonium chloride, Basic Blue 26, CI 44045),
N-{4-[(4'-diethylamino)phenyl]-[4"-(ethylamino)-1"-naphthyl]methylene}-2,5-cyclohexadien-1-ylidene)-N-ethylethanammonium chloride (Basic Blue 7; CI 42595),
4-[(4'-aminophenyl)-(4'-imino-2',5'-cyclohexadien-1'-ylidene)methyl}-2-methylaminobenzene hydrochloride (Basic Violet 14; CI 42510),

4-acetylamino)-5-hydroxy-6-{[7'-sulfo-4'-[(4''-sulfophenyl)azo]-1'-naphthyl)azo}-1,7-naphthalenedisulfonic acid tetrasodium salt (Brilliant Black 1; CI 28440),
[8-(p-aminophenyl)azo]-7-hydroxy-2-naphthyl]-trimethylammonium chloride (Basic Brown 16; CI 12250),
[8-(4'-amino-2'-nitrophenyl)azo]-7-hydroxy-2-naphthyl]trimethylammonium chloride (Basic Brown 17; CI 12251),
7-hydroxy-8-[(2'-methoxyphenyl)azo]-N,N,N-trimethyl-2-naphthylammonium chloride (Basic Red 76; CI 12245),
3-[(4'-amino-6'-bromo-5',8'-dihydro-1'-hydroxy-8'-imino-5'-keto-2'-naphthylamino]-N,N,N-trimethylammonium chloride (Basic Blue 99; CI 56059),
4-(3'-trimethylammoniumphenylazo)-N-phenyl-3-methyl-5-pyrazolone (Basic Yellow 57; CI 12719).

The quantities of the dyeing or coloring effector molecules, particularly of the hair dyes, preferably direct hair dyes, depend on the quantities used for dyeing hair which are known to those skilled in the art. The total quantity of the said effector molecules can range between 0.001 and 10.0 wt.% and particularly between 0.001 and 5.0 wt. %, based on the total quantity of the cosmetic agent.

The first component which can be referred to as the peptidic linker molecule comprises short-chain peptides which are preferably in the form of 3-mers to 30-mers and more particularly of 6-mers to 12-mers. Preferred are peptides containing amino acid derivatives with a free amino, hydroxyl or sulfanyl group, for example the derivatives of 3-amino-alanine, ornithine, lysine, serine, threonine, cysteine and homocysteine. Suitable are, for example, the following peptides: AKKNR KTDND DS, DDDDE SEHHA KT, DDDE EEE, DDDEE EDQKR SKKHR, DDDEE HHHR, DDDEE SEDES EEQ, DDEED EDPTK, ARKT, DDEEE EEDE, DDEEE RRHKK, DDEES EE, DDERH HK, DDEHR K, DDETD DDSEP, DEDDE EETDN TSDNT, DEEDD EQKHK ATRT, DEEDE ENKHH T, DEEDE TDDDE DNST, DEEEH HHH, DEETE DDKSR KQN, DEETK SHTSA DESS, DEKHH DKEE, DEKRT PQDTT LNQST, DETTQ TDKEE, EDDDS EPHHR SKQ, EDEED ENPT DES, EDDEE E, EEDDD EEE, EEDDE DDQHR NQ, EEDDP KKHH, EEDDS KRR, EEDED EDPKQ HLLRN, EEDEE D, EEDEE SHHHK, EEDSR RR, EEEDD EDDD, EEEDD NDQEE D, EEEDD TPEEE KEESK, EEEDE DD, EEEEE DSEDD, EEERK K, ESDED DDETQ PSTNT, ESEE EDPEE DE, HHKKH RTEED E, HHKRR KPESE EETS, HHKSR RRRHQ, HHRKE EE, HHRKK HRT, HHRKK K, HKKKE DDDD, HKRRH RRQKK QKS,

HRKKR KKRPE EDDER, HTSDK EH, KHHRK RRDED TEEQ, KHHRK RRRK, KHSSS TTNEE EEQ, KKHDE DS, KKHDD E, KKHHT HTKRR N, KKKHR SKSDD DDQ, KKKKR EEDDE, KKKKR KKHKN NS, KKKN HSKHH KSS, KKKRR HS, KKRTT HHNEE EN, KRHHK RRHKD TDEEN, KRRHH R, KRRRH, KKKTK TSAK, KRTSN QPEDE RTHSL, NEDD DESNE EQ, NHHRD EHDEH S, RKKHE NDQ, RKKHR HREDE DEEDQ, RKKSE EEN, RRHHD DEE, RRKEE D, RRKKH HH, RRRHH HPEED EDS, RRRHH KPRRA KH, RRRHH PRRK, RRTKK SHH, RTHHH DQEEE, SEETS SQTHHK ATQ, SHEDD H, SHEHH TED, SHHKK KHHH KTKA, SHKKR KSRRH K, SSKKT QTRRN KS, SSKKT HQNST AT, SRRRK KHHSH, TDDDD EPSED T, TDDE DDEDD TDPN,TEEDS DPKKK Q, TEKHD EKDD, TGGGH KPEED S, THHES DK, THHRR EEED, TKEKD H, TTDEN ETTED, TSEES HSADE T, TSKHH RPTSS EKTS.

It is possible to add to the agent of the invention other active substances, auxiliary agents and additives that are generally and commonly used in cosmetic products. Examples of these are thickeners (for example clays, starch, polyacrylic acid and the derivatives thereof, cellulose derivatives or alginates), other hair-care and skin-care agents (for ex-ample sugars, proteins, lanolin derivatives, vitamins or provitamins, for example biotin, vitamin C, tocopherols or D-panthenol), fat-reducing agents, inorganic or organic acids (for example lactic acid, citric acid, glycolic acid, phosphoric acid), preservatives (for ex-ample para-hydroxybenzoic acid esters), nonaqueous solvents, antioxidants (for example tocopherols or the esters thereof), dyes and fragrances or perfumes, UV light-absorbing inorganic particles or pigments or micropigments, particularly metal compounds or half-metal compounds in ionic, nonionic or oxidized form. The pigments can be present in this form individually or as mixtures or as individual mixed oxides or mixtures thereof, inclu-ding mixtures of mixed oxides and pure oxides. Examples of such pigments are titanium oxides (for example TiO_2), zinc oxides (for example ZnO), aluminum oxides (for example Al_2O_3), iron oxides (for example Fe_2O_3), manganese oxides (for example MnO), silicon oxides (for example SiO_2), silicates, cerium oxide, zirconium oxides (for example ZrO_2), barium sulfate ($BaSO_4$) or mixtures thereof. Suitable pigments and micropigments are commercially available, for example Hombitec® L5 (INCI designation: titanium dioxides) supplied by Merck.

In principle, persons skilled in the art know which additives, auxiliary agents and carriers are used in hair and skin cosmetics so that the more detailed comments are intended only as examples and only to provide additional illustration of the present invention. Otherwise,

the reader is referred to the abundant literature that describes the general make-up of cosmetic preparations and is well known to those skilled in the art.

The additives, auxiliary substances and carriers can be used in the usual quantities known to those skilled in the art and can be incorporated by methods that in and of them-selves are known.

Before the application, the first component, namely the peptidic linker, and the second component, namely the effector molecule, are linked together as described and form the high-affinity cosmetic agent of the invention, the finished commercial product possibly containing other common active substances, auxiliary agents and carriers.

The cosmetic agents of the invention can be in different application forms known for cosmetic skin and hair products, for example in the form of shampoos, lotions, rinses, dispersions, emulsions, gels, cream gels, creams, lotions [sic], shake mixtures, sprays, aerosols or foams.

The present invention will now be explained in greater detail by way of a dye as the effector molecule.

Example 1

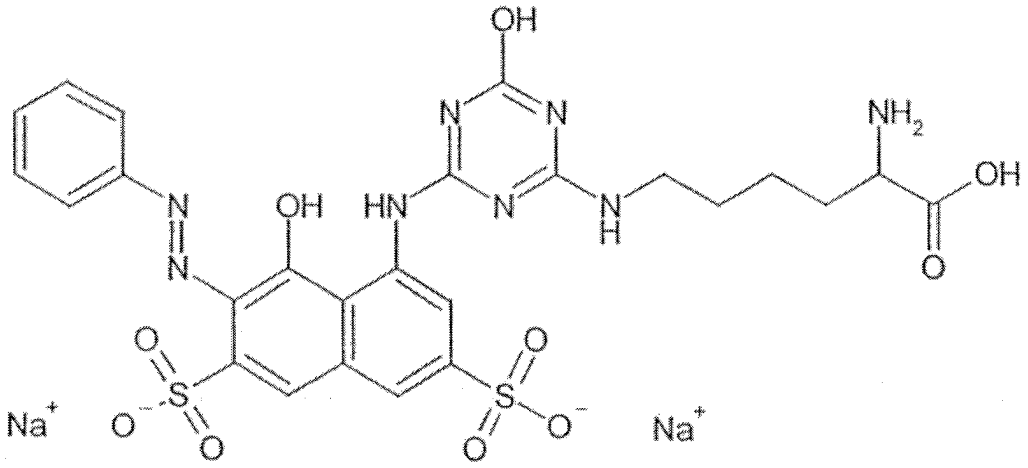
Preparation of 5-((4-((5-amino-5-carboxypentyl)amino)-6-hydroxy-1,3,5-triazin-2-yl)ami-no)-4-hydroxy-3-(phenylazo)-2,7-naphthalenedisulfonic acid disodium salt (formula III)

Step 1:

6.15 g (10 mmoles) of Reactive Red 2 (based on 100 % pure dye) and 2.0 g (11 mmoles) of D,L lysine hydrochloride were dissolved in water, and the pH was adjusted to 9 - 9.5 with 30 % NaOH. The solution was then heated to 40 °C and stirred for 6 hours while keeping the pH and temperature constant. The solution was then cooled to room tem-perature and 5-((4-((5-amino-5-carboxypentyl)amino)-6-chloro-1,3,5-triazin-2-yl)amino)-4-hydroxy-3-(phenylazo)-2,7-naphthalenedisulfonic acid disodium salt was precipitated by addition of methanol under conditions of crystallization.

Step 2:

The moist product from Step 1 was taken up in 20 mL of water, then 20 mL of 30 % of sodium hydroxide solution was added, and the reaction mixture was heated at 90°C. After 6 hours, the mixture was cooled, cautiously acidified to pH 4.5 with acetic acid, and the 5-((4-((5-amino-5-carboxypentyl)amino)-6-hydroxy-1,3,5-triazin-2-yl)amino)-4-hydroxy-3-(phenylazo)-2,7-naphthalene disulfonic acid disodium salt, formula III, was precipitated by addition of methanol (about 40 mL). After filtering and drying, 5.8 g of dye was obtained in the form of a red powder. The λ_{max} of the dye in water was 544 nm.



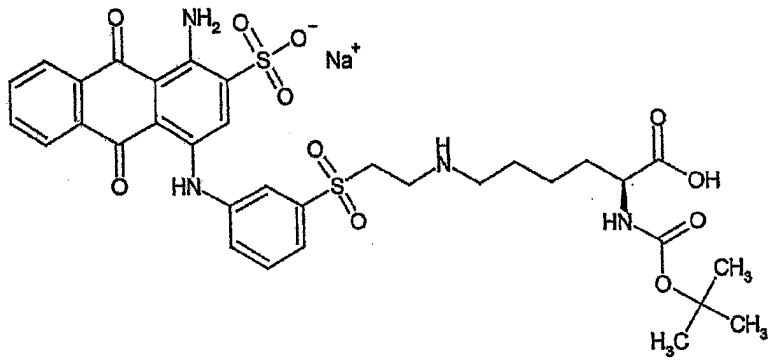
III

Example 2

Preparation of 1-amino-4-((3-((2-(((5S)-5-amino-5-carboxypentyl)amino)ethyl)sulfonyl)-phenyl)amino)-9,10-diketo-9,10-dihydro-2-anthracenesulfonic acid sodium salt (formula V)

Step 1

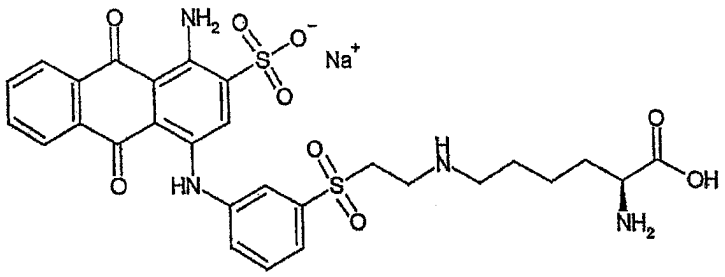
6.26 g (10 mmoles) of Reactive Blue 19 (based on 100 % pure dye) and 2.7 g (11 mmoles) of N(alpha)-BOC-L-lysine were dissolved in 30 mL of water, and the pH was adjusted to 9 - 9.5 with 30 % sodium hydroxide solution. The solution was then heated at 90°C for 6 hours while keeping the pH constant by addition of sodium hydroxide solution. The mixture was cooled to room temperature and cautiously acidified to pH 4.5 with acetic acid, and the reaction product was precipitated by addition of methanol (about 40 mL). After filtering and drying, 5.4 g (71 % of the theoretical) of 1-amino-4-((3-((2-(((5S)-5-(((1,1-dimethylethoxy)carbonyl)amino-5-carboxypentyl)amino)ethyl)-sulfonyl)phenyl)amino)-9,10-diketo-9,10-dihydro-2-anthracene sulfonic acid sodium salt was obtained as a blue powder.



IV

Step 2

2.0 g (2.6 mmoles) of the compound from Step 1 was stirred with 10 mL of hydrochloric acid (concentration: 1 mole/L) for 2 hours at room temperature. The dye was precipitated by addition of 20 mL of methanol. After filtering and drying, 1.4 g (82 % of the theoretical) of 1-amino-4-((3-((2-(((5S)-5-amino-5-carboxypentyl)amino)ethyl)-sulfonyl)phenyl)amino)-9,10-diketo-9,10-dihydro-2-anthracenesulfonic acid sodium salt was obtained as a blue powder. The λ_{max} of the dye in water was 598 nm.



V

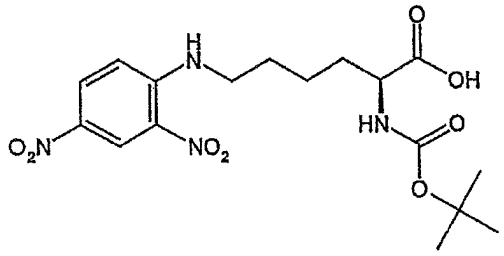
Example 3

Preparation of (2S)-2-amino-6-((2,4-dinitrophenyl)amino)hexanoic acid (N6-(2,4-dinitro-phenyl)-L-lysine)

Step 1

1.86 g (10 mmoles) of 2,4-dinitrofluorobenzene and 2.7 g (10 mmoles) of N(alpha)-BOC-L-lysine were heated in 30 mL of acetonitrile at 90 °C for 6 hours. After cooling of the batch

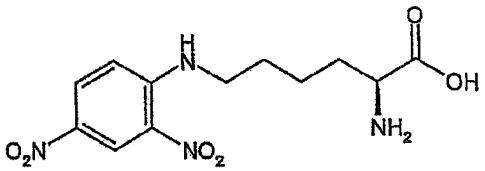
to room temperature, the acetonitrile was distilled off. This left a residue 4.1 g (99 % of the theoretical) of 6-((4-amino-2-nitrophenyl)amino)-(2S)-(((1,1-dimethylmethoxy)-carbonyl)amino)hexanoic acid (formula VI) as a bright yellow solid.



VI

Step 2

3.2 g (7.8 mmoles) of the compound from Step 1 was stirred in 10 mL of hydrochloric acid in dioxane (concentration: 3 moles/L) at room temperature for 3 hours. At the end of the reaction, the dye was precipitated by addition of 20 mL of diethyl ether. After filtering and drying, 2.1 g (95 % of the theoretical) of (2S)-2-amino-6-((2,4-dinitrophenyl)-amino)hexanoic acid (N6-(2,4-dinitrophenyl)-L-lysine (formula VII) was obtained as a bright yellow powder. The λ_{max} of the dye in ethanol/water (1 : 1) was 412 nm.



VII

ABSTRACT

The present invention relates to a cosmetic agent consisting essentially of a peptidic link-er and at least one cosmetic substance covalently connected therewith.

CLAIMS

1. Cosmetic agent comprising two components covalently connected to one another and having functions that are different from one another, wherein the first component is a peptidic linker molecule with high affinity or binding specificity for keratin-containing material and the second component is at least one cosmetic substance consisting of at least one known organic cosmetically active effector molecule.

2. Cosmetic agent characterized in that the cosmetic substance consists of at least one or of several different cosmetically active effector molecules.

3. Cosmetic agent as defined in claims 1 and 2, characterized in that the peptidic linker molecule has a chain length between 2 and 30 amino acids.

4. Cosmetic agent as defined in claims 1 to 3, characterized in that the cosmetically active effector molecule has dyeing or color-imparting, cosmetic care-imparting, conditioning, protective, hardening, softening, repairing and/or reconstituting properties.

5. Cosmetic agent as defined in claim 4, characterized in that the cosmetic effector molecule comprises at least one dye, hair-conditioning agent, combability improver, polymer, surfactant, amidoamine, betaine ester, Esterquat, silicone polyol, fatty alcohol, chitosan, moisturizer, vitamin, provitamin, vitamin precursor, springiness improver, betaine, sugar or UV filter.

6. Cosmetic agent as defined in claims 1 to 5, characterized in that more than one effector molecule is connected with the peptidic linker and that at least two different cosmetic activities are exhibited or that it has different peptidic linkers with bonding strengths of different magnitude for keratin-containing material and to which are attached different effector molecules, or that it has at least two different peptidic linkers that differ in terms of bonding strength and bonding site on the keratin-containing material.

7. Use of a cosmetic agent as defined in claims 1 to 6 for cosmetically treating keratin-containing material of humans and animals.

8. Use of a cosmetic agent as defined in claim 7, characterized in that the keratin-material is human or animal hair.

9. Use of a cosmetic agent as defined in claims 7 and 8, characterized in that the cosmetic material contains a dye as the effector molecule and is a hair-dyeing agent.

10. Use of a peptidic linker molecule and at least one organic cosmetically active effector molecule with dyeing or coloring, cosmetic care-imparting, conditioning, protective, hardening, softening, repairing and/or reconstructive properties for producing a cosmetic agent.

11. Use of a cosmetic agent as defined in claim 10, characterized in that the cosmetic agent is a hair-treatment agent.

12. Use of a cosmetic agent as defined in claims 10 and 11, characterized in that the effector molecule is a dye and the hair-treatment agent is a hair-dyeing agent.